PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 10 August 1999 (10.08.99)	
International application No. PCT/IL98/00592	**Applicant's or agent's file reference** 114508.5 MM
International filing date (day/month/year) 07 December 1998 (07.12.98)	**Priority date** (day/month/year) 07 December 1997 (07.12.97)
Applicant SHINITZKY, Meir et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

22 June 1999 (22.06.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

S. Mafla

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
REINHOLD COHN AND PARTNERS
P.O. Box 4060
61040 Tel-Aviv
ISRAEL

RECEIVED
04 -10- 1999
REINHOLD COHN & PARTNERS

PCT

WRITTEN OPINION

(PCT Rule 66)

WO

Date of mailing *(day/month/year)*	30.09.99
REPLY DUE	**within 3 month(s)** from the above date of mailing

Applicant's or agent's file reference	International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
114508.5 MM	PCT/IL98/00592	07/12/1998	07/12/1997

International Patent Classification (IPC) or both national classification and IPC
G01N33/68

Applicant
YEDA RESEARCH AND DEVELOPMENT CO. LTD. et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain document cited
VII	☒	Certain defects in the international application
VIII	☒	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 07/04/2000.

Name and mailing address of the international preliminary examining authority:
European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer / Examiner
Weijland, A

Formalities officer (incl. extension of time limits)
Houyez-Stevens, M
Telephone No. +49 89 2399 8163

I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".)*:

Description, pages:

1-13 as originally filed

Claims, No.:

1-10 as originally filed

Drawings, sheets:

1/1 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. This opinion has been established as if (some of) the amendments had not been made, since they have b en considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 2-6 (with respect to industrial applicability),

because:

☒ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

s separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1, 7-9 No
Inventive step (IS)	Claims	1, 7-9 No
Industrial applicability (IA)	Claims	

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

The following document is referred to in this communication; the numbering will be adhered to the rest of the procedure:

D1: WO 97 13152 A (YEDA RESEARCH AND DEVELOPMENT COMPANY LTD) 10 April 1997

POINT III

Claims 2-6 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT). For the assessment of such claims on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

POINT V

Novelty

D1 (abstract, example 3) describes an assay for the diagnosis of multinfarct and altzheimer dementia in an individual. It comprises the steps of obtaining a sample from an individual, a platelet containing fragment thereof, and determining the level of platelet associated antibody against a 75 kD platelet-protein in said sample. In example 3, the platelets from 60 blood donors were solubilized and separated by isoelectric focusing from pH 1.5 to 12.5 and collected in fractions. They identified a 75 kD protein in the fractions collected with a pI between pH 7 to pH 9.

Claim 1 is anticipated by D1, since D1 refers to a platelet derived protein preparation with a pI between 7 and 9.

Claim 7, referring to a kit, is also anticipated by D1 for similar reasons. The same

applies to claims 8 and 9.

Claim 10, referring to proteins with a pI higher than 6.5 are prepared from platelets obtained from the individual to be tested, is not mentioned in D1 and is novel according to Article 33(2) PCT.

The subject-matter of claims 2 to 6 is novel, since no methods are described in the prior art documents to detect schizophrenia in a subject using a platelet derived protein preparation.

Inventive Step

D1 is considered to be the closest prior art. Claim 10 differs from D1 in that the protein preparation has a pI above 6.5 and is prepared from platelets of the individual to be tested.

The skilled person, knowing of the teaching of D1, would not be motivated to prepare said protein preparation in diagnosis of schizophrenia. Therefore, claim 10 is inventive according to Article 33(3) PCT.

Claims 2, 4, 5 and 6 differ from D1 in that a diagnostic method for assaying schizophrenia in a subject is described using a platelet derived protein preparation and claim 3 differs from D1 in that it describes a method for the preparation of a reagent for use in the diagnosis of schizophrenia.

Such methods are not disclosed in the prior art documents. Moreover, its subject-matter cannot be deduced in an obvious way from these documents either if taken alone or in any combination.

Therefore, claims 2-6 involve an inventive step in accordance with Article 33(3) PCT.

POINT VII

On page 8 (second paragraph) of the description homologies are mentioned with the

pool 2 proteins. However, since no sequences of pool 2 proteins are disclosed it is inappropriate to discuss about homologies. Therefore, lines 9 and 10 should be deleted from the description.

D1 should be identified in the description and the relevant background art disclosed therein should be briefly discussed (Rule 5(a)(ii) PCT).

POINT VIII

The term "above about" mentioned in claim 1 renders the range unclear and should be corrected throughout the claims and the description to meet the requirements according to Article 6 PCT.

The upper limits of pI 10 on page 12 of the description (first paragraph) and 9.5 in claim 1 are in disagreement and render the scope of the claim unclear (Article 6 PCT).

The passage "As seen in the figure, a DTH response as explained above, was observed in the two schizophrenic patients.." (page 13 of the description, third paragraph) lacks clarity since figure 1 shows the result of only one patient and render the claimed subject-matter unclear (Article 6 PCT).

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
114508.5 MM		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IL98/00592	07/12/1998	07/12/1997
International Patent Classification (IPC) or national classification and IPC		
G01N33/68		
Applicant		
YEDA RESEARCH AND DEVELOPMENT CO. LTD. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 8 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22/06/1999	15.03.00
Name and mailing address of the international preliminary examining authority:	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Weijland, A Telephone No. +49 89 2399 7490

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IL98/00592

I. Basis of th report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1,4-7,9-11	as originally filed	
2,3,8,12,13	with telefax of	14/02/2000

Claims, No.:

1-10	with telefax of	14/02/2000

Drawings, sheets:

1/1	as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 7-10 (with respect to industrial applicability).

because:

☒ the said international application, or the said claims Nos. 7-10 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 1, 5, 6-10
	No:	Claims 2-4
Inventive step (IS)	Yes:	Claims 1, 5, 6-10
	No:	Claims 2-4
Industrial applicability (IA)	Yes:	Claims 1-6
	No:	Claims

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

se separate sheet

The following document is referred to in this report; the numbering will be adhered to the rest of the procedure:

D1: WO 97 13152 A (YEDA RESEARCH AND DEVELOPMENT COMPANY LTD) 10 April 1997

SECTION I

1. The amendments filed with the letter of 14. 02.2000 meet the requirements of Article 34(b) PCT.

SECTION III

2. Claims 7-10 are considered to be directed to diagnostic methods practised on the human body and therefore to relate to subject-matter considered by this authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

SECTION V

3. Novelty (Article 33(2) PCT)

3.1 D1 (abstract, example 3) describes an assay for the diagnosis of multi-infarct and Alzheimer dementia in an individual. It comprises the steps of obtaining a sample from an individual, a platelet containing fragment thereof, and determining the level of platelet associated antibody against a 75 kD platelet-protein in said sample. In example 3, the platelets from 60 blood donors were solubilized and separated by isoelectric focusing from pH 1.5 to 12.5 and collected in fractions. They identified a 75 kD protein in the fractions collected with a pI between pH 7 to pH 9.

Claim 2 is anticipated by D1, since D1 refers to a platelet derived protein preparation with a pI between 7 and 9. The features mentioned in (ii) and (iii) of claim 2 do not render the claim novel, since they are considered to be present

implicitly and are immaterial. Claims 3 and 4 are also anticipated by D1, since the platelet derived protein preparation has a pI between 7 and 9 isolated from a pool of 60 donors.

3.2 Claim 5, referring to proteins with a pI higher than 6.5 are prepared from platelets obtained from the individual to be tested, is not mentioned in D1 and is novel according to Article 33(2) PCT.

3.3 Claim 1 is directed to the use of a protein preparation comprising platelet derived proteins for diagnosis of schizophrenia by determining a Delayed Type Hypersensitivity reaction.

Claim 6 is directed to a method for the preparation of a reagent for use in the diagnosis of schizophrenia.

Claims 7, 8 and 9 are directed to diagnostic methods for determining schizophrenia.

Claim 10 is supposed to be dependent on claims 7-9 (see section VIII) .

The subject-matter of the said claims is novel, since no use of a protein preparation or methods are described in the prior art documents to detect schizophrenia in a subject based on platelet derived protein preparations.

4. Inventive Step (Article 33(3) PCT)

4.1 Claim 5 would appear to involve an inventive step.

D1 is considered to be the closest prior art. Claim 10 differs from D1 in that the protein preparation is prepared from platelets of the individual to be tested.

The skilled person, knowing of the teaching of D1, would not be motivated to prepare said protein preparation of the individual to be tested. This is not suggested in the prior art documents, either if taken alone or in any combination.

4.2 Claims 1, 6-10 would appear to involve an inventive step.

The methods, based on a platelet derived protein preparation, or use of this protein preparation to which the said claims are directed, are not suggested in the prior art documents and cannot be deduced in an obvious way from these documents either if taken alone or in any combination. The same applies to claim 10.

SECTION VIII

5. The term "above about" mentioned in claims 1, 2, 6, 7, 8 and 9 renders the subject matter for which protection is sought unclear (Article 6 PCT).

6. The dependencies of claim 10 is not clear (Article 6 PCT).

W. *Reduced suppressor cell function in psychiatric patients.* Ann. N.Y. Acad. Sci.. 1987; **396**; 686-690.

7. Mihalovic, L.J. and Jankovic B.D. *Effects of intraventricularly injected anti-caudatus antibody on the electrical activity of the cat brain.* Nature 1961; **192**; 665.
8. Rapport, M.M., Karplak, S.E. and Mahadik, S.P. *Biological activities of antibodies injected into the brain.* Fed. Proc. 1979; **38**; 2391.
9. Vartanian, M.E. Doyskina, G.S. Lozovsky, D.V., Burbaera, G.S. and Ignaton, S.A. *Aspects of humoral and cellular immunity in schizophrenia. In: Birth Defects. Original Article Series* D. Bergsma and A. Goldstein, eds. **vol 14**; 339-364; Alan R. Liss; New York, N.Y; 1978.
10. Rotman, A. *Blood platelets in psychopharmacological research.* Prog. Neuropsycopharmacol. 1983; **6**; 135-151.
11. Pletscher, A. *Biological Psychiatry*, Gea Racagni, ed; Elsevier Science Publisher; 1991; **2**, 354-356.
12. Shinitzky, M., Deckmann, M., Kessler, A., Sirota, P., Rabbs, A. and Elizur, A., *Platelet autoantibodies in dementia and schizophrenia - possible implications for mental disorders.* Ann. N.Y. Acad Sci. 1991; **621**; 205-217.
13. Kessler, A. and Shinitzky, M., *Platelets from schizophrenic patients bear autoantiboies that inhibit dopamine uptake.* Psychobiology 1993; **21**; 229-306.
14. PCT Patent Application WO 95/23970.
15. Shinitzky, M. *et al.*, WO 97/13152.
16. Deckmann *et al.*, *Italian Journal of Psychiatry and Behavioural Sciences*, **6**:29-34, 1996.

The above references will be acknowledged in the text below by indicating their number from the above list shown in brackets.

BACKGROUND OF THE INVENTION

Schizophrenia is a syndrome which encompasses a variety of symptoms including paranoia, auditory hallucination, delusions, catatonia, bizarre behavior and emotional withdrawal. Schizophrenia affects about 1% of the total population. Its economical and social burden on society is enormous since onset occurs in youth thus requiring patients to be under medical and psychiatric supervision for most of their lives. Schizophrenia is therefore one of the most costly diseases in the industrialized world.

Since the biochemical basis of schizophrenia has not yet been elucidated, diagnosis today is still based solely upon psychiatric evaluation. Furthermore, no therapy is currently available for schizophrenia although the symptoms may be ameliorated by neuroleptic drugs.

Many reports have implicated the immune system in the etiology and course of several mental disorders. Serum antibodies which cross-react with brain antigens have been found in the blood of schizophrenic patients[1–6], thus indicating that schizophrenia is also an autoimmune disease[7–9]. Furthermore, platelets have been used as a model for neuronal tissue[10,11] and elevated levels of autoantibodies to platelets have been detected in schizophrenic and demented patients, but not in patients suffering from manic-depressive disorder, depression, personality disorders or schizoaffective disorders[12-14]. An assay for the diagnosis of multi-infarct dementia and dementia of the Alzheimer type was described based on detection of a high level of a platelet associated antibody[15].

A cellular response against autologous platelets was also demonstrated in schizophrenia patients who showed a delayed type hypersensitivity (DTH) reaction when injected with platelets collected from their own blood[16].

It is therefore the object of the present invention to provide a test for the diagnosis of schizophrenia in a subject.

well as individual proteins, polypeptides or peptides among the Pool 2 proteins which are active in eliciting the DTH reaction in schizophrenic patients, are also an aspect of the invention.

The Pool 2 protein preparation prepared in accordance with the invention and used in the diagnostic methods of the invention include proteins purified from the Pool 2 proteins, polypeptides or peptides comprising sequences of such proteins, fractions thereof, as well as proteins, polypeptides or peptides obtained by synthesis or by genetic engineering having a sequence identical to that of the proteins of the Pool 2 proteins.

In accordance with the invention, Pool 2 proteins used in the diagnostic assay of the invention are such which are capable of eliciting DTH activity in an injected individual, the DTH activity being tested by the test known in the art. In short, the Pool 2 proteins are intradermally injected into the tested individual at the forearm or thigh and the reaction at the injection site is evaluated after 24, 48 and 72 hours by measuring the reaction diameter around the induration. As mentioned above, there may be cases in which the time profile of the reaction will differ from the typical time profile of a DTH reaction.

The present invention further provides a kit for use in diagnosis of schizophrenia, comprising said Pool 2 proteins, active protein fractions obtained therefrom, or individual active proteins or peptides, derived from said Pool 2 proteins. Preferably, such proteins are provided in either injectable form or in a form suitable for preparing an injectable formulation, e.g. a lyophilysate. Typically, the kit will be provided with instructions for use or a chart or pictures for guidance of the manner of scoring the results.

Example 2 Preparation of Pool 1 and Pool 2 proteins

Methods

Platelet suspension containing about 20 gr total protein was obtained as in Example 1, and the platelets solubilized with 40 ml of a solution containing 0.5% of the detergents NP-40 and Triton-X-100 for 5 mins. at room temperature with gentle shaking. The solution was then centrifuged at 4000 g for 15 mins. at 20°C. The supernatant was collected, and the pellet was subjected to two further extractions with 10 ml 0.1% Triton-X-100. The three supernatants were combined and Bio-Lyte Ampholyte™ 3/10 (40%) of BioRad was added to a final concentration of 1%. The solubilized proteins were subjected to isoelectric focusing. 60 ml of sample was applied to the Rotofor™ system of BioRad, using 0.1 M phosphoric acid as anode solution, and 0.1 M NaOH as cathode solution. The isoelectric focusing was performed for about 4 hours at 10°C using 10 Watt constant power until the current remained constant for 30 mins. Proteins were divided into two separate groups in accordance with their pI: proteins having a pI in the range of 2-6.5 are referred to as Pool 1 proteins while proteins having a pI in the range of 6.5-9.5 are referred to as Pool 2 proteins. Pool 1 and Pool 2 proteins were harvested separately and diluted 1:50 with PBS.

Example 3 Injection of Pool 1 and Pool 2 proteins

Method

The following four preparations were injected intradermally into the forearm of a schizophrenic patient:

i. Pool 2 proteins (marked as P2)

ii. Pool 1 proteins (marked as P1)

iii. Autologous platelets (marked A)

iv. PBS.

0.1 ml of each above preparation were injected and the preparations were injected at four different injection sites spaced about 10 cm from

each other. The skin reaction at each injection site was monitored 24 h, 48 h and 72 h after injection.

Results

The results are seen in Fig. 1 where (i) is the highest injection site on the arm and (iv) is the lowest.

As seen in the figure, a DTH response measured as explained above, was observed in a schizophrenic patient at the site of injection of Pool 2 proteins and no DTH reaction was seen at the site of P1 injection. Furthermore, the DTH reaction at the P2 site of injection was substantially enhanced as compared to the DTH reaction seen at the site of injection of the autologous platelets. Thus, it is, in most cases, preferred to use a P2 protein preparation obtained from a pool of blood samples obtained from several heterlogous individuals in the diagnostic assay of the invention.

CLAIMS:

1. Use of a protein preparation comprising platelet derived proteins or fractions thereof having an isoelectric point (pI) above about 6.5 and preferably within the range of above 6.5 to about 9.5, for the preparation of an injectable reagent for diagnosis of schizophrenia in an individual by determining a Delayed Type Hypersensitivity (DTH) reaction in said individual following injection of said reagent to the individual.

2. A kit for use in diagnosis of schizophrenia in an individual by detection of DTH reaction in said individual, comprising:

(i) a protein or a fraction thereof prepared from human platelets, said proteins or fractions thereof having a pI of above about 6.5;

(ii) a chart and/or pictures for guidance of the manner of scoring said DTH reaction; and

(iii) instructions for use.

3. A kit in accordance with Claim 6, wherein the proteins or fractions thereof have a pI within the range of above 6.5 to about 9.5.

4. A kit in accordance with Claims 6 or 7, wherein the proteins or fractions thereof are prepared from heterologous platelets obtained from a number of individuals other than the individual to be tested.

5. A kit in accordance with Claims 6 or 7, wherein the proteins or fractions thereof are prepared from autologous platelets obtained from the individual to be tested.

6. A method for the preparation of a reagent for use in diagnosis of schizophrenia in an individual by detecting a DTH reaction in said individual following injection of said reagent to the individual, comprising:

(a) obtaining blood samples from a number of individuals, preparing a pool from said samples and collecting platelets therefrom;

(b) preparing a protein fraction from said platelet preparation comprising proteins or fractions thereof having a pI of above about 6.5.

7. A diagnostic method for determining schizophrenia in a subject comprising:

(a) obtaining a preparation comprising, as an active component, platelet derived proteins or fractions thereof having a pI above about 6.5;

(b) injecting said preparation into a subject; and

(c) examining the subject for the occurrence of delayed type hypersensitivity reaction at the site of the injection, a positive result being a reaction above that which is observed in non-schizophrenic subjects, indicating that the subject has a high likelihood of being schizophrenic.

8. A diagnostic method for determining schizophrenia in a subject comprising:

(a) obtaining a blood sample from a number of schizophrenic and/or non schizophrenic individuals other than the tested subject and collecting platelets therefrom;

(b) preparing a protein fraction from said platelet separation comprising proteins or fractions thereof having a pI of above about 6.5;

(c) injecting said protein preparation into a subject; and

(d) examining the subject for the occurrence of a delayed type hypersensitivity reaction at the site of the injection, a positive result being a reaction above that which is observed in non-schizophrenic subjects, indicating that the subject has a high likelihood of being schizophrenic.

9. A diagnostic method for determining schizophrenia in a subject comprising:

(a) obtaining a blood sample from an individual and collecting platelets therefrom;

(b) collecting proteins or fractions thereof from said platelet sample, said proteins or fractions having a pI of above about 6.5.

(c) injecting said collected proteins or fractions thereof to the tested individual; and

(d) examining the subject for the occurrence of delayed type hypersensitivity reaction at the site of the injection, a positive result being a reaction above that which is observed in non-schizophrenic subjects, indicating that the subject has a high likelihood of being schizophrenic.

10. The method of any one of the previous claims, wherein said proteins or fractions thereof have a pI within the range of above 6.5 to about 9.5.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
114508.5 MM		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IL 98/00592	07/12/1998	07/12/1997
Applicant		
YEDA RESEARCH AND DEVELOPMENT CO. LTD. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 2 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[ ] the text is approved as submitted by the applicant.

[X] the text has been established by this Authority to read as follows:

SKIN TEST FOR SCHIZOPHRENIA

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1

[X] as suggested by the applicant.

[ ] None of the figures.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

PATENT COOPERATION TREAT

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
REINHOLD COHN AND PARTNERS
P.O. Box 4060
61040 Tel-Aviv
ISRAEL

RECEIVED
- 7 -05- 1999
REINHOLD COHN & PARTNERS

Applicant's or agent's file reference 114508.5 MM	Date of mailing *(day/month/year)* 03/05/1999
International application No. PCT/IL 98/00592	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
Applicant YEDA RESEARCH AND DEVELOPMENT CO. LTD. et al.	International filing date *(day/month/year)* 07/12/1998

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Cornelis Hurenkamp

Form PCT/ISA/220 (July 1998)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
114508.5 MM		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IL 98/00592	07/12/1998	07/12/1997
Applicant		
YEDA RESEARCH AND DEVELOPMENT CO. LTD. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 2 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   SKIN TEST FOR SCHIZOPHRENIA

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1

   [X] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IL 98/00592

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 G01N33/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 13152 A (YEDA RESEARCH AND DEVELOPMENT COMPANY LTD) 10 April 1997 see page 12, line 10 - line 23; claims 1-4	1,3,7-10
Y		1-10

Y	BIOLOGICAL ABSTRACTS, vol. 82, Philadelphia, PA, US; abstract no. 24088, XP002100216 see abstract & G. SH. BURBAEA ET AL.: "The Arthus reaction and delayed hypersensitivity reaction to neurospecific proteins S-100 and 10-40-4 in schizophrenic patients." ZK NEVROPATOL PSIKHIATR IM S S KORSAKOVA, vol. 86, no. 1, 1986, pages 193-195, Moscow RUS	1-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 April 1999	03/05/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Van Bohemen, C

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IL 98/00592

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9713152 A	10-04-1997	AU 6999296 A	28-04-1997
		CA 2233321 A	10-04-1997
		EP 0856158 A	05-08-1998

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

REINHOLD COHN AND PARTNERS
P.O. Box 4060
61040 Tel-Aviv
ISRAEL

RECEIVED
21-03-2000
REINHOLD COHN & PARTNERS

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Applicant's or agent's file reference 114508.5 MM	Date of mailing *(day/month/year)* 15.03.00
	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IL98/00592	07/12/1998	07/12/1997

Applicant
YEDA RESEARCH AND DEVELOPMENT CO. LTD. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Digiusto, M Tel.+49 89 2399-8162

Form PCT/IPEA/416 (July 1992)